American Journal of Medical Genetics 66:154–162 (1996)

Osteoglophonic Dysplasia: Review and Further Delineation of the Syndrome

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We report on a boy with clinical and radiologic findings of osteoglophonic dysplasia. He had craniostenosis, "bizarre," expansile cystic lesions in the diaphyses, delayed tooth eruption, and progressive rib expansion typical of the syndrome. Initially delayed psychomotor development with later normal intelligence, early feeding and breathing difficulty, and speech delay are also characteristic of the disorder. Manifestations, not previously reported in osteoglophonic dysplasia, present in the propositus are spontaneous fractures resulting in pseudoarthroses through cystic and dysplastic foci in his proximal femoral shafts and right humerus, pretibial dimples, hypospadias, marked rib expansion, and absence of significant vertebral abnormality. These findings expand the spectrum of osteoglophonic dysplasia. © 1996 Wiley-Liss, Inc.

KEY WORDS: osteoglophonic dysplasia, osteoglyphic dysplasia, skeletal dysplasia, craniostenosis

INTRODUCTION

Osteoglophonic dysplasia is a rare skeletal dysplasia syndrome characterized by distinct bone lesions, disproportionate dwarfism, and severe craniofacial defect. The syndrome was first described by Fairbank in 1958 as a case report of "acrocephaly with abnormalities of the extremities" and Keats et al. as "craniofacial dysostosis with fibrous metaphyseal defects." Spranger [see Beighton et al., 1980] coined the term osteoglophonic dysplasia, derived from Greek and meaning "hollowed out," for this syndrome.

Received for publication June 30, 1995; revision received January 17, 1996.

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Affected individuals have an abnormal skull shape at birth with associated craniostenosis, feeding problems, nasal obstruction or respiratory complications in infancy, failure to thrive, rhizomelic dwarfism, and lucent lesions in the bones [Fairbank, 1959; Keats et al., 1975; Beighton, 1980; Kelley et al., 1983; Santos et al., 1988; Stöß et al., 1991; Gorlin et al., 1990]. We report on an affected boy whose pretibial dimples and fractures with development of pseudarthroses through areas of lucent bone were manifestations not reported previously.

CLINICAL REPORT

The propositus was delivered in breech position by Caesarian section following a pregnancy complicated by hyperemesis gravidarum in the first trimester and maternal hepatitis with high fever in the 3rd gestational month. Maternal weight gain was 3.6 kg. Apgar scores were 3 and 6 at 1 and 5 minutes, respectively. At birth, short bowed limbs, pretibial dimples, small scapulae, and hypoplastic toenails were noted. Because of severe respiratory distress, he was intubated and ventilated. Birth weight was 2,430 g (10th centile), length was 43.5 cm (below 4 S.D.), and OFC was 31.4 cm (below 2.5 S.D.) (Fig. 1). Craniofacial findings included large anterior and posterior fontannels, open sagittal and metopic sutures, proptosis, hypertelorism, short nose with depressed bridge, anteverted nares, long philtrum with carp-shaped mouth, and large protruding tongue. He had second degree hypospadias and undescended left testicle. Skeletal involvement consisted of proximally shortened upper limbs and bowed lower limbs with bilateral tibial dimples. At 1 month, a tracheostomy tube was placed and at 3 months, a gastrostomy feeding tube was placed. The infant remained hospitalized for 6 months. Subsequently, he had multiple hospital admissions for suspected fractures, and once each for subluxation of the eyeball and pneumonia. Serum calcium, phosphorus and alkaline phosphatase levels were normal.

At 44 months of age his length was 67 cm (50th centile for 6–8 months), weight was 7.2 kg, and OFC and

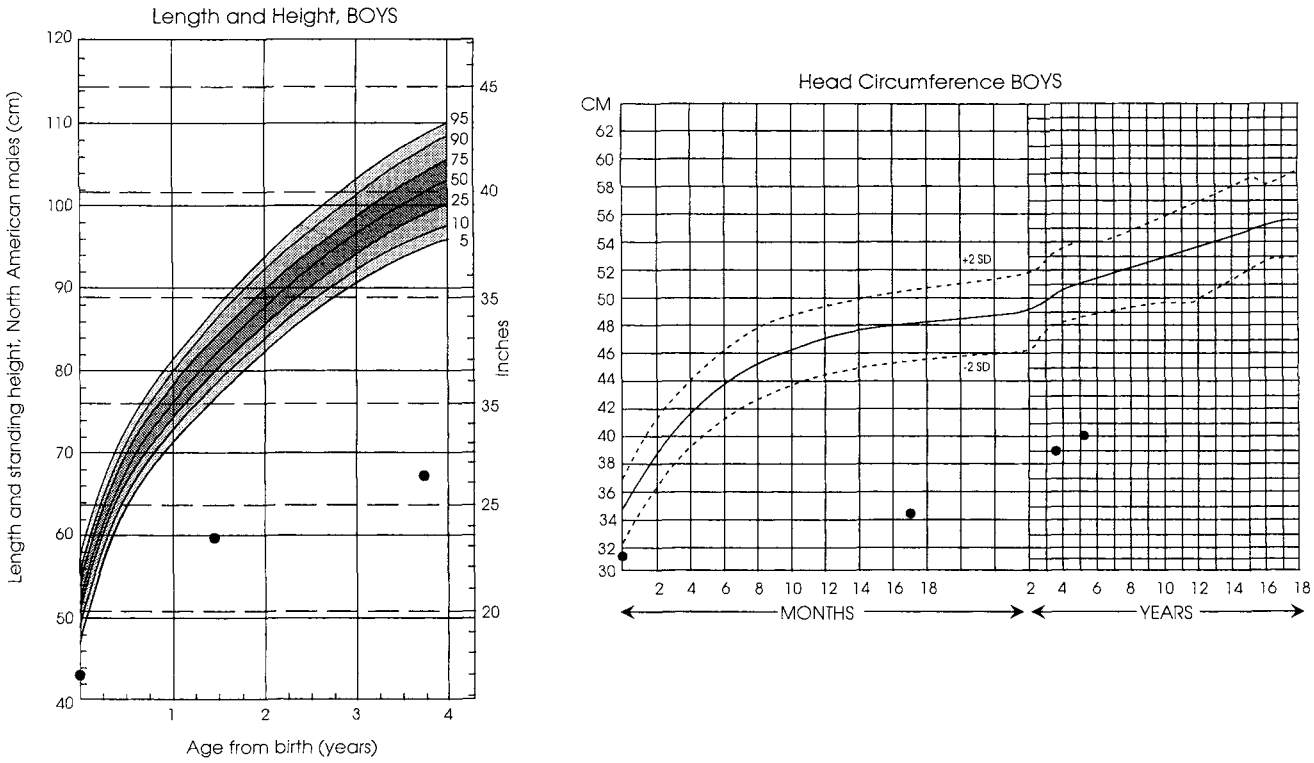

Fig. 1. Growth charts.

39 cm (Fig.1). He had a Kleeblattschädel deformity, frontal bossing, marked proptosis, downslanted palpebral fissures, a large, protruding tongue, full and dependent cheeks, and no teeth (Fig. 2). His ears were apparently low-set and the helices "crumpled." He was tracheostomy dependent. He had short and broad hands and feet, short and bowed limbs, and bilateral tibial dimples. He was fully dependent, non-ambulatory, and non-verbal, but seemed to have good receptive abilities.

He attended a preschool program for the mentally retarded. At C.A. 58 months, adaptive function (Vineland) ranged from 10 to 23 months, but cognitive function by non-verbal testing (Leiter) showed an IQ of 103 (Table I). During the past 2 years of follow-up, he has begun ambulating with a walker, and remains tracheostomy-dependent, which limits expressive language. Several teeth have erupted but have broken off at the gum line. There has been chronic gingivitis. He has been placed in an inclusion program where he has made academic progress.

The mother was a 33-year-old G5P2 woman and father was 33 years old at the time of his birth. They are unrelated African Americans. A son, 3 years older than the affected child, and another, 1.5 years younger, are in good health. The father's half-brother was described as "short" in stature with "spine problems."

RADIOGRAPHIC FINDINGS

At birth, the propositus had short, bowed limbs, and small scapulae (Figs. 3, 4a). The craniofacial malformation is characterized by extremely shallow orbits, midface hypoplasia, synostosis of the sagittal and both coronal sutures, and nasal inlet obstruction (Fig. 5). The teeth were unerupted (Fig. 5e-f).

Serial radiographs demonstrated an evolving skeletal dysplasia, characterized by marked rib expansion (Fig. 4) and cystic and dysplastic foci in the diaphyses of most of the long bones (Figs. 6, 7). Spontaneous fractures resulting in pseudoarthroses occurred through cystic and dysplastic foci in the proximal femoral shafts and right humerus (Figs. 6, 7).

DISCUSSION

The overall radiologic pattern of osteoglophonic dysplasia is distinctive; however, individual manifestations reminiscent of campomelic dysplasia (bowing of long bones), fibrous dysplasia (cystic expansile lesions of the diaphyses), neurofibromatosis (pseudoarthroses), and lysosomal storage disorders (rib expansion) were seen in this patient. The initial clinical and radiologic impression was "campomelic dysplasia with atypical findings." However, there were several anomalies not typical of campomelic dysplasia, including an apparently normal spine, shallow orbits, midface hypoplasia, and craniostenosis. The severe respiratory distress,

Fig. 2. **a,b:** The propositus at 3 years 10 months. Note turribrachycephaly, frontal prominence, crumpled ears, hypertelorism, proptosis, anteverted nares, depressed nasal bridge, large tongue, and rhizomelia. **c:** Note tibial dimple (arrow).

TABLE I. Cognitive Function at C.A. 4 Years 10 Months

Leiter international performance scale	Mental age	IQ
	5 years 0 months	103
Vineland adaptive behavior scales	**Rating scale**	**Mental age**
	Communication skills	1 year 2 months
	Daily living skills	1 year 6 months
	Socialization skills	1 year 11 months
	Motor skills	10 months

which necessitated intubation soon after birth, was initially ascribed to tracheomalacia, a common finding in campomelic dysplasia. However, an intrinsic tracheal abnormality could not be confirmed. In retrospect, the respiratory distress was probably due to nasal obstruction. A similar clinical and radiologic course has been seen in previous cases of osteoglophonic dysplasia (Table II) [Fairbank, 1959; Keats et al., 1975; Beighton, 1980; Kelley et al., 1983; Santos et al., 1988; Reynolds, 1988; Stöß et al., 1991]. This is the first patient with fractures and pseudarthroses. It is unclear why these occurred. Interestingly, in patients surviving into adulthood, the osteolytic defects resolve [Fairbank, 1951, Kelley et al., 1983]. This patient had an apparently normal spine, while platyspondyly is more com-

Fig. 3. **a,b:** Limbs in newborn period. Note short-bowed femur, tibia, and fibula (a); note the barrel-shaped phalanges (b).

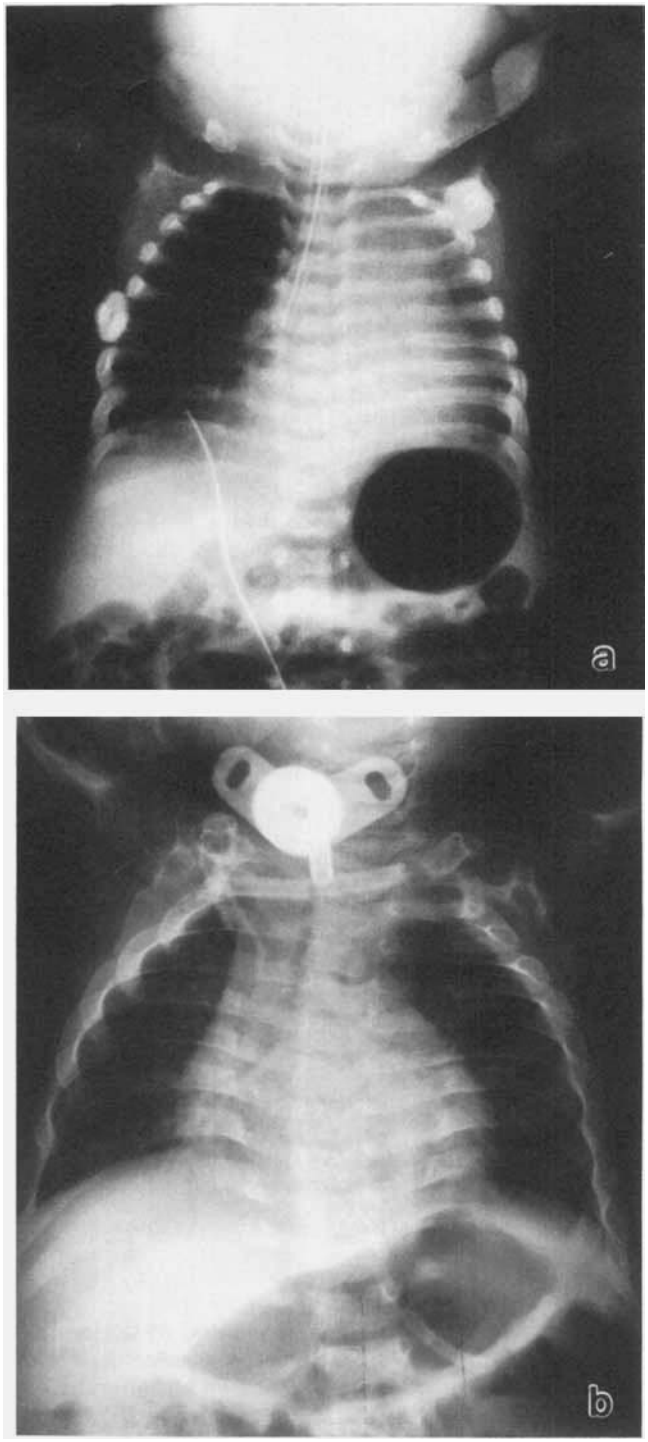

Fig. 4. Chest. **a:** Newborn, normal ribs and spine. **b:** 1 year 5 months, broadened ribs and normal vertebrae.

monly described [Beighton, 1980; Kelley et al., 1983; Santos et al., 1988; Stöß et al., 1991].

Despite psychomotor delay in childhood, intelligence generally is normal. Two adults reportedly worked as a draftsman and a machinist, respectively [Fairbank, 1975; Kelley et al., 1983]. Because of significant psychomotor delay and inability to speak, our patient was thought to be mentally retarded. Non-verbal intelligence testing led to placement in an appropriate educational setting which has been beneficial.

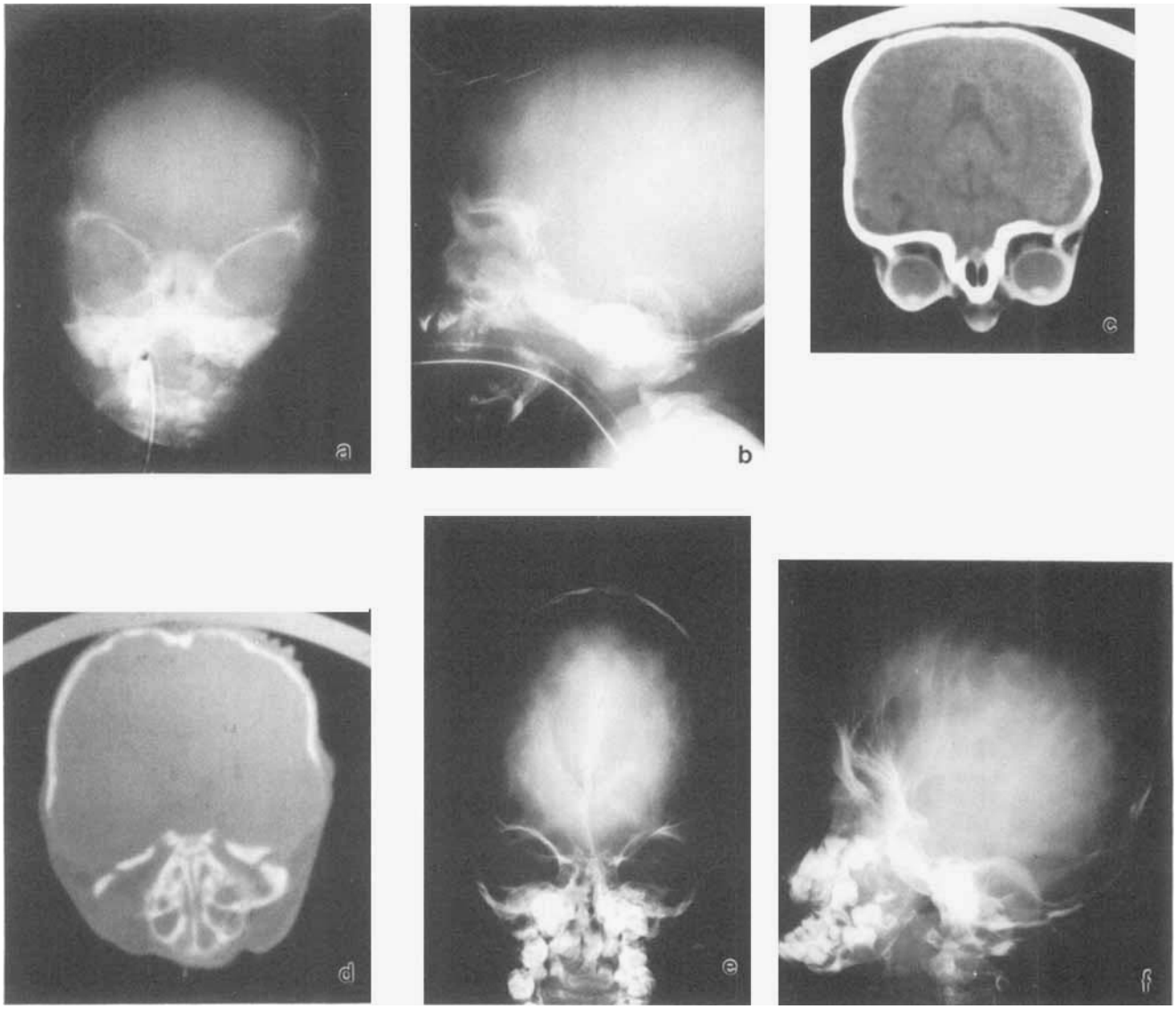

Fig. 5. **a,b:** AP and lateral skull films on day 4 showing slight oxycephaly, and "harlequin" orbits (a) and shallow deformed orbits (b). **c,d:** CT 2 months. A cut through the orbits demonstrates very shallow orbits (c). A cut through the nasal cavity shows marked narrowing of the anterior nasal cavity (d). **e,f:** Skull films 4 years 4 months illustrating coronal and sagittal synostosis and unerupted teeth.

Life expectancy appears to be related to the craniofacial malformations, which have been associated with respiratory and feeding problems. Two patients died in infancy, one at 10 days and the other at 10 months [Santos et al., 1988; Stöß et al., 1991]. Another patient died at age 27 of pneumonia [Gorlin et al., 1990].

Although not common, genitourinary malformation may be present. Cryptorchidism and inguinal hernia were noted by Kelley [1983] and our patient had hypospadias and chordee.

Pathological correlation was limited to two patients. Biopsy of a lucent area in one patient demonstrated benign, whorled fibrous connective tissue [Keats, 1975]. Autopsy of a 10-day-old affected infant of 36 weeks gestation, who died of respiratory insufficiency is reported by Stöß et al., 1991.

Osteoglophonic dysplasia has occurred sporadically in both sexes. Father to son transmission consistent with autosomal dominant inheritance occurred in two families [Kelley et al., 1983; Reynolds et al., 1988].

Osteoglophonic dysplasia has been classified both as a craniostenosis syndrome and as a skeletal dysplasia. Significant advances have occurred in the molecular characterization of these syndromes. Defects in several collagen genes have been found in a number of skeletal dysplasias [Prockop and Kivirikko, 1995], but these are not associated with craniostenosis. Recently, three skeletal dysplasias, as well as four craniostenosis syn-

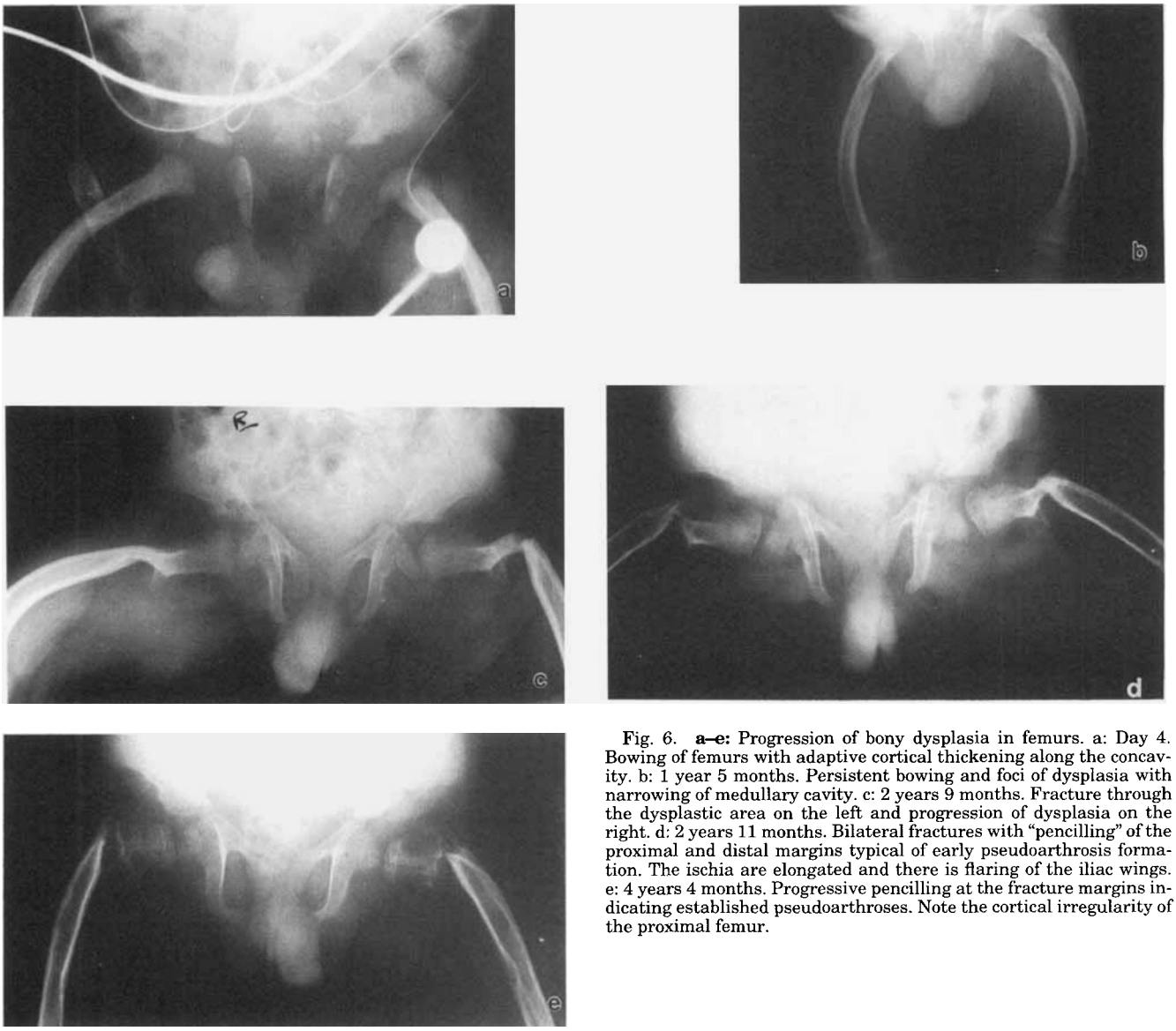

Fig. 6. **a–e:** Progression of bony dysplasia in femurs. a: Day 4. Bowing of femurs with adaptive cortical thickening along the concavity. b: 1 year 5 months. Persistent bowing and foci of dysplasia with narrowing of medullary cavity. c: 2 years 9 months. Fracture through the dysplastic area on the left and progression of dysplasia on the right. d: 2 years 11 months. Bilateral fractures with "pencilling" of the proximal and distal margins typical of early pseudoarthrosis formation. The ischia are elongated and there is flaring of the iliac wings. e: 4 years 4 months. Progressive pencilling at the fracture margins indicating established pseudoarthroses. Note the cortical irregularity of the proximal femur.

Fig. 7. **a:** 2 years 1 month. Progression of dysplasia in long bones. Note bowing of the tibia and marked expansion of medullary cavity and thinning of cortex of both bones. Compare to Figure 3a. **b:** Right humerus. Note cystic foci with pathologic fracture, which subsequently developed into pseudoarthrosis.

dromes have been found to have mutations in fibroblast growth factor receptors [Park et al., 1995]. A common molecular defect in the fibroblast growth factor receptor-3 (FGFR3) on chromosome 4 has been reported in people with achondroplasia [Shiang et al., 1994; Rousseau et al., 1994]. FGFR3 is also the locus for hypochondroplasia [Bellus et al., 1995] and for thanatophoric dwarfism [Tavormina et al., 1995]. Crouzon, Apert, and Jackson-Weiss syndromes are the result of mutations in the fibroblast growth factor receptor-2 (FGFR2) on chromosome 10 [Reardon et al., 1994; Wilkie et al., 1995; Jabs et al., 1994]. In Pfeiffer syndrome mutations have been found in both the fibroblast growth factor receptor-1 on chromosome 8, and the FGFR2 [Muenke et al., 1994; Schell et al., 1995]. This suggests that since osteoglophonic dysplasia is a skeletal dysplasia with craniostenosis, a defect in a fibroblast growth factor receptor is a likely. Studies of these receptors should be undertaken.

ACKNOWLEDGMENTS

This study was supported by the New York State Office of Mental Retardation and Developmental Disabilities. It was presented in part at the annual meeting of the American Society of Human Genetics, 1994 [Am J Hum Gen 55:A78, 1994]. The authors thank Leslie Gulick, M.D. of the Department of Pediatrics, SUNY Health Science Center at Brooklyn, and the family for their participation.

TABLE II. Summary of Published and Present Cases of Osteoglophonic Dysplasia

Clinical manifestations	Fairbank, 1959	Keats et al., 1975	Beighton et al., 1980	Kelley et al., 1983 Case 1	Kelley et al., 1983 Case 2	Santos et al., 1988	Stöß et al., 1991	Present case
Birth weight	?	7 lb 5 oz	2,750 g	4,054 g	?	4,140 g	1,840 g	2,430 g
Birth length			49.5 cm	49.5 cm		48.5 cm	37 cm	43.5 cm
Abnormal skull shape at birth	+	+	+	+	+	+	+	+
Nasal obstruction/ breathing difficulty	+	+	+	+	+	+	+	+
Feeding difficulty	+	+	+	+	+	+	+	+
Failure to thrive	+	+	+	+	+	+	+	+
Craniostenosis	+	Coronal	Sagittal, metatropic	Kleeblatschadel	Kleeblatschadel	Coronal	Coronal	Sagittal and coronal
Cystic metaphyseal defects	+	+	+	+	+	+	+	+
Rhizomelic dwarfism	+	+	+	+	+	+	+	+
Proptosis	?	+	−	+	−	+		+
Hypertelorism	?	?	+	+	+	+	+	+
Frontal bossing	?	Sloping	+	?	?	+	+	+
Developmental delay	?	?	+	+	+	+		+
Normal intelligence	+	+	+	?	+	?		+
Unerupted teeth	?	+	+	+	+	+		+
Anteverted nares	?	?	+	+	+	+		+
Vertebrae	?	Posterior scalloping	Platyspondyly anterior beaking	Platyspondyly anterior beaking	?	Platyspondyly	Platyspondyly	Normal
Prognathism	?	+	+	+	+	+		+
Genitourinary abnormalities	−	−	−	Cryptorchidism inguinal herniae	Inguinal herniae	−	−	Hypospadias and chordee

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